

REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1, 3-4, 11-28, 41, 62 and 63, the only claims pending and under examination.

FORMAL MATTERS

Claims 1, 3, 4, 11-28, 41, 62 and 63 have been examined and rejected.

Claims 29-40, and 42-61 have been previously withdrawn.

Claims 2 and 5-10 have been canceled.

Accordingly, no new matter has been added. As no new matter has been added by the above amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 3, 4, 13, 14, 16, 18-22, 28, 41, 62 and 63 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297).

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007))); and see *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (citing *KSR Int'l Co.* at 1741)); and see *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must

determine "[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references," (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

In rejecting the present claims, the Examiner has noted (Office Action, p. 8), "Gambardella et al. does not explicitly teach that modulating the autonomic nervous system results in substantially equal parasympathetic or sympathetic functions in at least a portion of said autonomic nervous system."

However, the Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention that oral administration of propranolol modulates or balances the sympathetic and parasympathetic activities of the autonomic nervous system in cancer patients because when balancing such activities a stage is assertedly reached where sympathetic and parasympathetic activities are substantially equal. (Office Action, p 8-9).

The Applicants respectfully disagree. In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must demonstrate that the prior art reference teaches or suggest all the claimed limitations. The Office has not pointed to where Gambardella discloses achieving substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Gambardella fails to teach or suggest this element because the method in Gambardella discloses the use of propranolol in elderly weight-losing cancer patients to block the effects of the sympathetic nervous system. The goal of treatment disclosed in Gambardella is enhancement of daily caloric intake without increased energy expenditure (abstract).

After administering propranolol, a decrease in energy expenditure is noted (Fig. 2), indicating a decrease in the basal metabolic rate (BMR) in these patients.

It is entirely possible that in treating weight-losing patients with propranolol as in Gambardella, the desired treatment goal of a decrease in BMR could be achieved before reaching a situation where the sympathetic and parasympathetic activity is substantially equal. In other words, a patient could be successfully treated with propranolol, resulting in a measured decrease in energy expenditure or BMR, without ever achieving a stage where the sympathetic and parasympathetic function is substantially equal.

Gambardella therefore fails to teach the element of treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

Furthermore, with respect to Claim 18, Gambardella does not teach or suggest a method of treating a subject for a condition caused by an autonomic nervous system abnormality wherein the abnormality comprises an abnormally low parasympathetic activity with normal sympathetic activity. The Examiner has stated that Gambardella “does not explicitly teach a method of treating conditions caused by abnormality in autonomic nervous system wherein the abnormality is characterized by normal sympathetic activity.” (Office Action, p. 4). The Examiner further states that it would have been obvious to administer a beta-blocker such as propranolol in treating a condition where the abnormality is characterized by normal sympathetic activity, and that the motivation to do so is provided by Gambardella because the reference teaches that propranolol is effective in the treatment of abnormality of the autonomic nervous system (Office Action, p. 4)

However, the Applicants respectfully disagree. It would not have been obvious in view of Gambardella to administer a beta-blocker such as propranolol in treating a

condition where the abnormality is characterized by normal sympathetic activity, because Gambardella discloses the use of propranolol to block the effects of sympathetic bias in weight-losing cancer patients. Nowhere in Gambardella is there disclosed the element of using a beta-blocker for a condition characterized by normal sympathetic activity.

In addition, with respect to Claim 63, Gambardella does not teach or suggest a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of the autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein the method further comprises increasing parasympathetic activity. Gambardella does not teach or suggest this element because Gambardella discloses the use of propranolol to block the effects of the sympathetic nervous system in weight-losing cancer patients. Nowhere in Gambardella is the element of increasing parasympathetic activity.

Therefore, a prima facie case of obviousness has not been established because Gambardella fails to teach or suggest all the elements of the rejected claims. Namely, Gambardella does not specifically disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Furthermore, as discussed above, Gambardella fails to teach or suggest the element of treating an abnormality with normal sympathetic activity, as in dependent Claim 18, nor does Gambardella teach or suggest the element of treating an abnormality by increasing parasympathetic activity, as in dependent Claim 63. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 3, 4, 13, 14, 16, 18-22, 28, 41, 62 and 63 be withdrawn.

Claims 1, 3, 4, 21, 28, and 41 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Brevetti et al. (Brief communications, Nov. 1981, p 938-941).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

In making this rejection, the Examiner states that the reference teaches a sympathetic bias and a parasympathetic bias in at least a portion of the nervous system (Office Action, p. 5).

The Applicants respectfully disagree. In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must demonstrate that the prior art reference teaches or suggest all the claimed limitations. The Office has not pointed to where Brevetti discloses achieving substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Brevetti discloses treatment of an imbalance between the alpha- and beta-adrenoreceptor activity of the sympathetic nervous system (p. 941), however there is no discussion in Brevetti of the parasympathetic nervous system. Nowhere in Brevetti is there the element of modulating of the autonomic nervous system which results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

Therefore, a prima facie case of obviousness has not been established because Brevetti fails to teach or suggest all the elements of the rejected claims. Namely, Brevetti does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 3, 4, 21, 28, and 41 be withdrawn.

Claims 1 and 21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Nordling et al. (E Urol, 1992, 21, 328-331).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

In making this rejection, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention that administration of propranolol modulates or alters the sympathetic and parasympathetic activities of the autonomic nervous system by treating urethral inflammation and when balancing such activities a stage is reached where sympathetic and parasympathetic activities are substantially equal (Office Action, p. 6).

The Applicants respectfully disagree. The Office has not pointed to where Nordling discloses achieving substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Nordling discloses the blockage of beta-adrenergic receptors of the sympathetic nervous system, however nowhere in Nordling is there a discussion of the parasympathetic nervous system.

Furthermore, it is entirely possible that in treating urethral inflammation with propranolol as in Nordling, the desired treatment goal of a decrease in inflammation could be achieved before reaching a situation where the sympathetic and parasympathetic activity is substantially equal. In other words, treatment with propranolol could result in a decrease in inflammation, without ever achieving a stage where the sympathetic and parasympathetic function is substantially equal.

Therefore, a prima facie case of obviousness has not been established because Nordling fails to teach or suggest all the elements of the rejected claims. Namely, Nordling does not disclose treating a condition wherein modulating of the autonomic

nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1 and 21 be withdrawn.

Claims 1, 3, 4, 11-12, 15, 17, 21 and 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Majcherczyk et al. (Br J Pharmacol, 1987, 91(4), 711-4).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

In making this rejection, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention that administration of propranolol modulates or alters the sympathetic and parasympathetic activities of the autonomic nervous system in the treatment of hypertension and when balancing such activities a stage is reached where sympathetic and parasympathetic activities are substantially equal (Office Action, p. 6).

The Applicants respectfully disagree. In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must demonstrate that the prior art reference teaches or suggest all the claimed limitations. The Office has not pointed to where Majcherczyk discloses achieving substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Majcherczyk discloses that after treatment with beta-blockers, the activity in the renal sympathetic nerve is increased (p. 711), which argues against the hypothesis that the antihypertensive effect of beta-blockers is due to general sympathetic inhibition to all vascular areas (p. 713). The disclosure in Majcherczyk, therefore, is directed to the mechanism of action of beta-blockers in treating hypertension. Majcherczyk does not discuss effects on the

parasympathetic nervous system, and nowhere in Majcherczyk is there the element of modulating of the autonomic nervous system which results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

Furthermore, with respect to Claim 17, Majcherczyk does not teach or suggest a method of treating a subject for a condition caused by an autonomic nervous system abnormality wherein the abnormality comprises an abnormally low parasympathetic activity with an abnormally low sympathetic activity. The Examiner has stated that the reference "inherently teaches....a low sympathetic activity" (Office Action, p. 6), however the Examiner has not pointed to where Majcherczyk discloses treatment for a condition with an abnormally low sympathetic activity.

Additionally, with respect to Claim 22, Majcherczyk does not disclose the element of increasing the parasympathetic activity/ sympathetic activity ratio in at least a portion of the autonomic nervous system. Majcherczyk does not disclose this element because Majcherczyk does not discuss the parasympathetic activity, and does not disclose the element of a parasympathetic activity/ sympathetic activity ratio.

Therefore, a prima facie case of obviousness has not been established because Majcherczyk fails to teach or suggest all the elements of the rejected claims. Namely, Majcherczyk does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. In addition, Majcherczyk does not teach or suggest a method of treating a subject for a condition caused by an autonomic nervous system abnormality wherein the abnormality comprises an abnormally low parasympathetic activity with an abnormally low sympathetic activity, as in Claim 17, nor does Majcherczyk disclose the element of increasing the parasympathetic activity/ sympathetic activity ratio in at least a portion of the autonomic nervous system, as in Claim 22. Consequently, the Applicants respectfully request that

the 35 U.S.C. § 103(a) rejection of Claims 1, 3, 4, 11-12, 15, 17, 21 and 22 be withdrawn.

Claims 1, 21, 23-25, and 28 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Davies, et al. (The J of Intl Med Research, 1988, 16, 173-181).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

In making this rejection, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention that administration of propranolol modulates or alters the sympathetic and parasympathetic activities of the autonomic nervous system in the treatment of hypertension and when balancing such activities a stage is reached where sympathetic and parasympathetic activities are substantially equal and that the reference teach that parasympathetic nerves influence cerebral blood flow during hypertension (Office Action, p. 7).

The Applicants, however, respectfully disagree. In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must demonstrate that the prior art reference teaches or suggest all the claimed limitations. The Office has not pointed to where Davies discloses achieving substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Davies discloses that ibuprofen does not substantially affect treatment of hypertension in patients on beta-blockers or thiazides, however there is no discussion in Davies of the autonomic nervous system. Nowhere in Davies is there the element of modulating of the autonomic nervous system which results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

Therefore, a prima facie case of obviousness has not been established because Davies fails to teach or suggest all the elements of the rejected claims. Namely, Davies does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 21, 23-25, and 28 be withdrawn.

Claims 1 and 26-27 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hill, et al. (U.S. Patent 6,449,507).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

In making this rejection, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention that administration of propranolol modulates or alters the sympathetic and parasympathetic activities of the autonomic nervous system as Hill teaches the stimulation of parasympathetic and sympathetic nerve fibers and when balancing such activities a stage is reached where sympathetic and parasympathetic activities are substantially equal.

The Applicants respectfully disagree. Hill discloses a method for adjusting the beating of the heart to allow a medical procedure to be performed, in which the heart rate may be increased or decreased. There is no disclosure in Hill that teaches or suggests that the process of increasing or decreasing the heart rate during a medical procedure will result in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. In other words, a patient could have a successful operation using the methods in Hill, without ever achieving a stage where the sympathetic and parasympathetic function is substantially equal.

Therefore, a prima facie case of obviousness has not been established because Hill fails to teach or suggest all the elements of the rejected claims. Namely, Hill does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1 and 26-27 be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number PALO-002.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 28, 2008

By: /Lynn Kidder, Reg. No. 56,107/
Lynn Kidder
Registration No. 56,107

Date: January 28, 2008

By: /Bret Field, Reg. No. 37,620/
Bret Field
Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231